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PATENT
454310-5010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAOLETTI, ET AL.	)	
	)	
v.	)	Interference 103,399
	)	
MOSS, ET AL.	)	Administrative Patent Judge Andrew H. Metz
	)	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231, BOX INTERFERENCE
on 18Apr95

THOMAS J. KOWALSKI, REG. NO. 32,147
Name of Applicant, Assignee or Registered Representative

Thomas J. Kowalski
Signature

18 Apr 95
Date of Signature

530 Fifth Avenue
New York, New York 10036

DECLARATION OF ENZO PAOLETTI

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

Sir:

I, Enzo Paoletti, declare and say that:

1. I executed a Declaration on February 27, 1995 captioned:

IN THE EUROPEAN PATENT OFFICE

In re: European Patent No.: 0 011 385 B1

European Appln. No.: 83 111976.3

Applicant/Proprietor: United States of America, as represented by the Secretary, United States Department of Commerce

(hereinafter "the European Opposition Declaration").

2. I am advised and therefore believe that a copy of the European Opposition Declaration was filed by Paoletti et al. in the above-captioned Interference. I have read and understood the European Opposition Declaration, hereby incorporate it herein by reference, and, adopt the European Opposition Declaration as testimony in the Interference. I am further advised and therefore believe that the Paoletti Et Al. Motion Under 37 C.F.R. §§ 1.633 And 1.637 For Judgement On Ground That Moss Et. al. Claims Not Patentable To Moss Et Al. ("the Paoletti Motion") cites the Abstracts and presentations of the September 20-23, 1982 Poxvirus-Iridovirus Workshop held at Cold Spring Harbor Laboratory, Cold Spring Harbor, New York ("the September 20-23, 1992 Workshop"), especially the Abstracts at pages 55, 40 and 59 (copy of each attached) and, had a copy of the Abstracts from the September 20-23, 1982 Workshop attached as an Exhibit (Exhibit 4 and included in Exhibit 21). I am also advised and therefore believe that Moss et al. has moved to strike or suppress those Abstracts as allegedly not authenticated. I hereby confirm that

the Abstracts from the September 20-23, 1982 Workshop attached to the Paoletti Motion and submitted as document D4 in the European Opposition were a true copy of the Abstracts of the September 20-23, 1982 Workshop received by me in the ordinary course of business, at registration for the September 20-23, 1982 Workshop prior to any meetings of the September 20-23, 1982 Workshop and, that since the September 20-23, 1982 Workshop, I have maintained the Abstracts from the September 20-23, 1982 Workshop in my custody and control in the ordinary course of business. Thus, the copy of the Abstracts from the September 20-23, 1982 Workshop attached to the Paoletti Motion and submitted as document D4 in the European Opposition are indeed a genuine, authentic copy of the Abstracts from the September 20-23, 1982 Workshop, publicly distributed at registration for and prior to any meeting of, the September 20-23, 1982 Workshop; and, that the copy of the Abstracts at pages 55, 40 and 59 attached hereto are indeed a genuine, authentic copy of the Abstracts at pages 55, 40 and 59 of the Abstracts from the September 20-23, 1982 Workshop, publicly distributed at registration for and prior to any meeting of, the September 20-23, 1982 Workshop.

3. I further declare that all statements made herein and in the European Opposition Declaration (herein by incorporation by reference) are true and that all statements made on information and belief are believed to be true; and, that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon or any Patent or application involved in the Interference.

Date: April 7, 1995

Enzo Paoletti

POXVIRUSES AS EUKARYOTIC CLONING VECTORS: D. Panicali and E. Paoletti, Center for Laboratories and Research, New York State Department of Health, Albany, NY

Recombinant vaccinia viruses expressing the thymidine kinase gene from Herpes simplex virus (HSV) or the hemaglutinin gene from influenza virus have been constructed and characterized. The foreign gene was first inserted into a non-essential genetic locus of contiguous vaccinia virus DNA sequences cloned in pBR322. These donor chimeric plasmids were introduced as calcium orthophosphate precipitates into eukaryotic tissue culture cells, previously infected with infectious virus. Site specific in vivo recombination allowed incorporation of the foreign DNA into the genome of replicating virus. Progeny virus containing the foreign gene were obtained as purified populations by several procedures.

The HSV-TK was incorporated into both the 120 Md prototypic L variant genome, as well as into the S variant, a spontaneous deletion mutant. When rescuing virus was TK^-, recombinants expressing HSV-TK were selected on TK^- cells in the presence of methotrexate. When rescuing virus was TK^+, recombinant vaccinia viruses expressing HSV-TK were detected by the specific utilization of ^{125}I-deoxycytidine (IDC). The endogenous vaccinia TK as well as the TK from a variety of eukaryotic cells failed to utilize IDC as substrate. Recombinant vaccinia viruses containing foreign genetic elements were additionally selected by a novel replica filter plating technique developed in our laboratory. This methodology is independent of expression or biochemical selectability of the foreign gene product and provides a general and rapid procedure for detection and recovery of viral vectors containing foreign genetic elements.

Restriction analysis of progeny recombinant viral DNA demonstrated the insertion and stable integration as a very specific event. Transcriptional analysis of the HSV-TK gene was consistent with the utilization of endogenous vaccinia promoters.

In addition to the foreign genes described above, other foreign DNA sequences have been introduced into recombinant vaccinia viruses including segments of hepatitis B virus. As much as 20 Kbp of foreign DNA have been stably inserted into recombinant vaccinia viruses as an attempt to determine the upper limit of foreign DNA packaging by the virus.

Exhibit B

NUCLEOTIDE SEQUENCES OF FIVE VACCINIA VIRUS EARLY GENES.

S. Venkatesan, M. Haffey, B. M. Baroudy, and B. Moss.
Laboratory of Biology of Viruses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205.

Regulatory elements discovered as consensus sequences are located upstream of transcriptional initiation sites of eukaryotic and prokaryotic genes. An unusually A•T-rich sequence has been found before a vaccinia virus gene specifying an early 7.5K polypeptide (Venkatesan, Baroudy and Moss, Cell 125, 805, 1981). To distinguish common and variable structural features, we have now sequenced five additional early genes. Three of the sequenced genes are located within the 10,000 bp inverted terminal repetition and were found to encode early mRNAs of about 1,000, 600, and 1,050 nucleotides that directed in vitro syntnesis of 7.5K, 19K, and 42K polypeptides respectively. Two other early genes are located between 16,000 and 18,000 bp from the left end of the genome and were found to encode mRNAs of about 760 and 880 nucleotides that directed in vitro synthesis of 14K and 32K polypeptides. The sixth gene specifies thymidine kinase and will be presented separately. Previous studies established that none of these mRNAs are spliced and in several cases, the capped ends were shown to be sites of transcriptional initiations. Genome fragments were cloned in plasmid or single-stranded DNA phage vectors and sequenced by the Maxam-Gilbert technique employing a novel "deletion-linker" strategy and/or by the Sanger dideoxynucleotide method. Several approaches including nuclease S1 analysis, primed reverse transcription of mRNAs, cDNA sequencing, and analysis of mRNA ends were used to determine the genomic location of the 5' or 3' ends of the messages. Common features of the early genes include extremely A•T-rich 40 to 60 bp segments immediately upstream of the transcriptional initiation sites, uninterrupted coding sequences, absence of eukaryotic poly(A) signal sequence, and multiple closely spaced 5' and 3' ends of transcripts. Distances between transcriptional and translational initiation sites and translational and transcriptional termination sites were quite variable. In some cases, genes were closely spaced with as little as 10 bp between the end of one and the start of another suggesting overlapping of regulatory sequences for initiation and termination of transcription.

Exhibit B

IDENTIFICATION AND NUCLEOTIDE SEQUENCE OF THE THYMIDINE KINASE GENE OF WILD-TYPE VACCINIA VIRUS AND NONSENSE MUTANTS. Jerry M. Weir, Gyorgy Bajszar, and B. Moss
Laboratory of Biology of Viruses, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland 20205.

The thymidine kinase (TK) gene has been mapped within the HindIII J fragment of vaccinia virus DNA (Weir, Bajszar and Moss, Proc. Natl. Acad. Sci. USA, 79, 1210, 1982). Further investigations revealed that enzymatically active TK was made in reticulocyte lysates programmed with early vaccinia mRNA that hybridized to plasmid recombinants containing either of two adjacent small DNA subsegments of the viral HindIII J fragment. The map position of an early polypeptide, with a molecular weight of about 19,000 (19K), coincided precisely with that of the TK. The absence of the 19K polypeptide in cell-free translation products of hybridization-selected mRNAs from several TK$^-$ mutants provided an independent identification of the TK polypeptide. The small size of the TK polypeptide of vaccinia virus distinguishes it from that of prokaryotes, eukaryotes and herpesvirus. RNAs of 590 and 2,380 nucleotides with 5' coterminal ends represent major and minor forms, respectively, of the TK message. The TK genes of wild-type and 3 putative nonsense mutants were cloned and sequenced by the dideoxynucleotide chain termination method. In each of the mutant DNAs, an extra nucleotide identical to one preceding it had been added. Because of the frameshift, a nonsense codon was introduced downstream. The region preceding the transcriptional initiation site of the TK gene is AT-rich and shares some sequence homology with similar regions of other early genes. Interestingly, the putative transcriptional regulatory region of the TK gene lies within the coding sequence of an adjacent late gene. Moreover, the 3' end of the late transcript overlaps the TK gene.

Exhibit B

Exhibit printed on 11/14/95

08/228,926

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European Patent Office

Munich

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The United States of America as...
Opp. 01: Virogenetics Corporation
Our Ref.: F 653 EP/Opp.

September 29, 1995
Ba/Jae/Wa/SF/idl

This is in response to the petition of the Patentee dated August 22, 1994.

Enclosed please find the following enclosures in duplicate:

(D29) Declaration by Dr. Paoletti
(D30) Declaration by Dr. Hruby
(D31) Declaration by Dr. Dales
(D32) Declaration by Dr. Aubertin
(D33) Declaration by Dr. Perkus
(D34) Declaration by Dr. Tartaglia
(D35) Declaration by Mr. Kowalski
(D36) Binns et al., WO 89/12684
(D37) Paoletti et al., US-A-4,769,330
(D38) Priority document to EP-A-0 083 286

1. INTRODUCTION

In the following, we will show that Patentee's assertions regarding patentability of the alleged invention are based on a factual misinterpretation of the prior art, a misunderstanding of the Opponent's line of argument as well as a misapprehension of the legal standards under which the EPO assesses patentability of an invention.

Our demonstration that none of the claims of the contested patent is patentable in the light of the prior art or for insufficiency of disclosure concentrates on claim 1. This is because the assertions made by the Patentee in his petition of August 22, 1994, are essentially a discussion of the invention as reflected by claim 1.

2. PATENTABILITY OF THE CLAIMED INVENTION

2.1 CLAIM 1

Claim 1 relates to a vector

(a) which can undergo homologous recombination in a pox virus; comprising
(b) a chimeric gene which
    (ba) comprises at least one pox virus transcriptional regulatory sequence; and
    (bb) under the transcriptional control of the regulatory sequence at least one uninterrupted protein coding sequence from a foreign gene;

(c) wherein the regulatory sequence and the coding sequence are not separated by another transcriptional regulatory sequence; and
(d) DNA, flanking the chimeric gene, from a non-essential region of the pox virus genome.

2.1.1 **Novelty of claim 1**

Despite the citation of an additional 18 documents for defending patentability of his invention, Patentee has not been able to convincingly refute our arguments for lack of novelty, inventive step and sufficiency of disclosure as set forth in our opposition brief of November 18, 1993.

This becomes immediately apparent when assessing novelty of claim 1. Patentee has tried to counterargue against our definition of the term "transcriptional regulatory sequence"; see page 8, penultimate paragraph et seq. According to Patentee, a "transcriptional regulatory sequence" (TRS) is, in brief, a sequence that regulates transcription anywhere in a living cell, organism or virus, irrespective of its actual biological context. In other words, even if the transcription machinery of a specific cell does not and can never recognise a DNA sequence that functions in another cell as a TRS, Patentee still regards this DNA sequence as a TRS in said specific cell. We again emphasise that such a definition is not tenable. A DNA sequence that is unable to transmit regulation of transcription is simply not a TRS. Thus, the recombinant vaccinia isolates vP2, vP4 and vP6 disclosed, for example, in Panicali (D3)

comprise an element that acts in an HSV environment as a promoter. These isolates were found to express the HSV gene as a foreign gene. From this data alone, the person skilled in the art might deduce that that element is a TRS that functions in vaccinia. However, Panicali and Paoletti have carried out additional experiments and have generated isolates vP1, vP3 and vP5. These isolates comprise the same foreign DNA, only in opposite orientation. No expression of the foreign gene was observed. The conclusion from these experiments is clear: the element could not and did not positively regulate transcription in either isolate. It, therefore, is no TRS in vaccinia but simply a piece of intervening DNA without a specific function.

Further support for our position comes from the following: As was well known at the priority date of the contested patent, a TRS is, due to the variety of possible primary sequences thereof, defined by its function and not only by its primary DNA sequence. We presume that Patentee would agree that the sequence TATAAT which serves as a promoter when located at a certain position 5' of the coding region of a eukaryotic gene, is not a promoter when located inside the coding region of said gene. Similarly, a DNA sequence that serves as a promoter of the HSV TK gene in herpes simplex virus cannot serve this function when introduced into a vaccinia virus.

If we transfer the above considerations to the experimental data obtained in the prior art, in particular the work conducted by Panicali and Paoletti (Panicali D3 and the first priority

document of Paoletti D7) the person skilled in the art would only draw one valuable conclusion, namely that the DNA sequence functioning as a TRS in HSV was not a TRS when introduced into a vaccinia virus. In this regard, it is further important to note that HSV replicates in the nucleus versus replication by vaccinia virus in the cytoplasm, such that upon observing expression in vP2, vP4 and vP6 versus vP1, vP3 and vP5, the skilled artisan knowing the replication differences would have further known that the extraneous, exogenous DNA in vP2, vP4 and vP6 was non-functioning (because HSV promoters do not function in the cytoplasm); and therefore there is no intervening "promoter" or TRS in vP2, vP4 and vP6.

Additionally, it is important to note that D7 does not teach that the HSV promoter must be present for successful expression as asserted by the patentee. As can be unumbiguously deduced from the priority document of D7, exactly corresponding to US-4,769,330, said document speaks of and teaches insertion of the "HSV TK gene" (i.e., the HSV TK coding sequence without any "HSV promoter sites") into the HindIII F-fragment (see, e.g., col. 9, line 63 to col. 10, line 10). The '330 Patent distinguishes the "HSV TK gene" from the "Bam HSV TK fragment"; the latter containing the HSV TK gene and extraneous non-functioning DNA (as to vaccinia virus), the former not including that extraneous non-functioning DNA (note that only the "Bam HSV TK fragment" is identified as having that DNA, not also the "HSV TK gene"). Thus, the '330 patent is not teaching any requirement that one must also insert any HSV promoter sites that do exist

whithin the "Bam HSV TK fragment" (note too that they are identified in the '330 Patent not as a "promoter" but rather, as "HSV promoter sites", indicating that they are DNA which functions as and therefore is a promoter in HSV but not in vaccinia virus). Thus, USSN 334,456 discloses in its general teachings as an exemplary embodiment inserting HSV TK gene into the HindIII F-fragment without the "HSV promoter sites", analogous to vP22.

2.1.1.1 Requesting that these consideration be kept in mind we would now like to draw the Opposition Division's attention to Table I which compares the features of claim 1 with the disclosure content of Paoletti (D7) (a document citable under Article 54(3)(4) EPC) and its first priority document, respectively.

TABLE I

Feature of Claim 1	Corresponding Disclosure content in D7	Disclosed in 1st priority document at
a vector	D7 discloses plasmid vector pDP 137; see, for example, page 27, second paragraph	p. 25, second paragraph
(a)	D7 discloses at page 31, 1st paragraph that "the 'foreign' DNA introduced into the S-variant has, at both ends of the DNA chain, a region of DNA which is homologous with corresponding sequences in the S-variant". This is exactly what the person skilled in the art considers homologous recombination in a pox virus.	p. 28, lines 15 to 17
(b)	D7 discloses the coding region of the HSV TK gene being driven by a vaccinia TRS; see our discussion of features (ba) and (bb) for more detailed information; this is what is understood by Patentee as a chimeric gene.	see below, discussion of features (ba) and (bb)
(ba) and (bb)	D7 states, starting at page 28, 7th line from the bottom of the page: "The direction of inclusion of the Bam HSV TK fragment within the vaccinia Hind III F-fragment may be important in case promotion of the description of the HSV TK is initiated by a promoter site within the F-fragment itself. However, promoter sites exist within the Bam HSV TK fragment itself, so that transcription of the HSV TK gene may occur no matter in which direction the Bam HSV	p. 26, first paragraph

	TK fragment and the HSV TK gene have been incorporated within the vaccinia Hind III F-fragment." Transcription of the HSV TK gene did only occur, if a certain direction of the HSV TK fragment occurred, namely that in pDP 137. Transcription was therefore not independent of the direction of incorporation of the HSV TK fragment within the Hind III F-fragment. Consequently, Paoletti and Panicali concluded on page 32, first paragraph that the "HSV TK-modified F-fragment is incorporated into the vaccinia variants in the cell and is capable of replication and expression under vaccinia control." [1,2,3] Therefore, features (ba) and (bb) are fulfilled by D7.	page 30, lines 1 to 4
(c)	No other sequence between the HSV coding sequence and the vaccinia TRS regulates transcription of said coding region; see conclusion in the discussion of features (ba) and (bb); accordingly, feature (c) is also fulfilled.	see above, discussion of features (ba) and (bb)
(d)	D7 discloses, on page 8 starting at line 4, that "the introduction of exogenous DNA thereinto must be non-essential to the viability and stability of the host; in this case the vaccinia virus". Thus, feature (d) is also fulfilled, in particular since the examples have shown growth, i.e. viability of the vaccinia virus.[4]	page 8, starting at line 4

1. In this regard Patentee's statement on page 3, 1st paragraph of his petition: "D9 (the US patent issued on the priority document discussed here) discloses that the inserted HSV TK gene must contain its own herpes promoter in order to obtain transcriptional expression. See D9 at column 9, lines 1-5" is definitely wrong and misleading.

2 Patentee's discussion with regard to the Panicali and Paoletti constructs on page 3, 2nd paragraph is without merit: it is totally irrelevant, if the vaccinia promoter was "fortuitously-proximal" to the foreign gene expressed. Claim 1 merely requires that the protein coding region of the foreign gene is under the control of the pox virus transcriptional regulatory sequence. Exactly this has been disclosed by Panicali and Paoletti in Panicali (D3) and Paoletti (D7).

3 At page 4, last paragraph, Patentee complains about our alleged lack of guidance, how a vaccinia TRS, such as the TK promoter might be identified. Such identification, was, for the person skilled in the art, at the priority date of the alleged invention a mere routine measure; please be referred to sections 18 to 29 of the enclosed declaration of Dr. Hruby for further guidance.

4 The Patentee has stated at the bottom of page 3 that he has so far missed our discussion of the fact that the alleged invention allows expression of a foreign gene in any non-essential region of any pox virus. We find this statement rather surprising: first, the contested patent, has, according to our knowledge not shown insertion of any gene in any virus with the exception of vaccinia virus. Therefore, the broad patent claims are not supported by the description; see section 2.1.3, infra. Second, the above quotation from D7 is self-explanatory and is certainly interpreted by the skilled person in the art that any non-essential region may be employed for insertion of the foreign gene.

In view of the above, we believe that the Opposition Division will readily acknowledge lack of novelty of claim 1 in view of the disclosure content of Paoletti (D7).

2.1.1.2 Lack of Novelty of Claim 1 is not, however, only conferred by the disclosure content of Paoletti D7. The detailed analysis of Panicali D3 (which is a document citable under Article 54(2) EPC) yields exactly the same result. We refer the Opposition Division for a sustantiation of our arguments to the following Table II.

TABLE II

Feature of Claim 1	Corresponding Disclosure content in D3
a vector	D3 also describes vector pDP 137; see page 4928, Figure 1.
(a)	In vivo recombination occurs between the flanking vaccinia virus DNA sequences and homologous sequences present in the replicating vaccinia virus genome; see page 4928, 1st paragraph of Results section.
(b)	The insertion of foreign DNA into infectious progeny vaccinia virus involves the formation of recombinant DNA containing the foreign gene flanked by contiguous vaccinia virus genomic sequences; see page 4928, 1st paragraph of the Results section.
(ba) and (bb)	D3 refers at page 4931, top, to the fact that "other (unpublished) data suggests that vaccinia signals may be operative for HSV TK expression"; accordingly, the vaccinia TRS is responsible for the expression of a foreign HSV TK gene.
(c)	From the discussion of features (ba) and (bb) necessarily followed at the priorty date of the contested patent that the DNA sequence operative in HSV as TK promoter is no TRS in vaccinia virus.
(d)	The insertion of foreign DNA into infectious progeny vaccinia virus involves the formation of recombinant DNA containing the foreign gene flanked by contiguous vaccinia virus genomic sequences; see page 4928, 1st paragraph of the results section; further, at the same page, next paragraph, D3 reports that "insertion of foreign genes into vaccinia virus must occur at loci that do not disrupt essential gene funtions".

Thus, from Table II it unambiguously follows that all the features of claim 1 are also disclosed by Panicali D3. Panicali D3 is therefore also novelty destroying for the main claim of the contested patent.

2.1.1.3 Lack of Novelty of claim 1 finally is also immediately apparent from the enclosed Declarations of Drs. Paoletti, Hruby, Dales, Aubertin, Perkus and Tartaglia (D29-D34).

Declarants state that Dr. Mackett presented data showing expression of a foreign gene under vaccinia control in a vaccinia based vector at both the ASV conference of August 2-4, 1982 and the CSH conference of September 20 to September 23, 1982. These declarations are further corroborated by the enclosed Declaration by Mr. Kowalski (D35), see, in particular the correspondence with Dr. Mackett, displayed therein as Exhibit B.

The declarations lead to only one conclusion, namely that Dr. Mackett indeed presented the data, that were later found suitable to file a patent application (which eventually, before the European Patent Office, led to the contested patent) and were published in the 1982 December issue of PNAS. Furthermore, since Patentee has not presented a single piece of convincing evidence demonstrating the contrary, it is believed that these two presentations by Dr. Mackett are indeed novelty destroying for claim 1.

This is all the more true since, from the declarations it can further be unambiguously

deduced that the presentations were not considered confidential. Additionally, due to this lack of confidentiality, the abstracts presented at the CSH meeting discussed in detail in Section 4.4 of our opposition are prior art for the alleged invention and a bar to patentability of claim 1. In this regard, we would particularly draw the Opposition Divisions attention to the enclosed Declaration by Dr. Samuel Dales (D31), who was a founder and organiser of the Pox Virus-Irido Virus workshop at Cold Spring Harbour. In this function Dr. Dales is probably in the best position to make a statement on the confidentiality of data presented in these meetings. Interestingly, Dr. Dales states that at the 1982 meeting, there was no obligation of confidentiality. Thus, the standards laid down in the decision T877/90 by the Technical Board of Appeal fully apply, to the disadvantage of Patentee. As the learned Opposition Division will know, in this decision the Board held that the content of an oral disclosure is made available to the public if, at the relevant date, it was possible for skilled persons as members of the public to gain knowledge of the content of the disclosure and if there was no bar of confidentiality restricting the use or dissemination of such knowledge.

Unfortunately for Patentee, the 1 year grace period for disclosures of the inventor applicable under US law which would cover the damages of a prior oral publication for a US patent application is not applicable under EPC regulations. As a consequence, said disclosures by Dr. Mackett are fully citable as prior art in

accordance with Article 54(2) EPC. (Naturally, the further abstracts cited in our opposition brief representing work from Dr. Paoletti's laboratory are prior art in any case, due to the lack of confidentiality of data presented at the CSH meeting).

Dr. Panicali (whose declaration is cited by Patentee as D15) merely states that he cannot remember anything worthwhile being presented at those meetings with regard to the expression of foreign genes in vaccinia based vectors under the control of vaccinia TRS. We are not in the least surprised by Dr. Panicali's statement and believe that it is perfectly true. Instead, we would have been rather surprised, if he had considered the data presented by Dr. Mackett extraordinary in view of the fact that he himself had previously published data to the same effect, for example, in Panicali D3 and, further, had filed together with Dr. Paoletti a US patent application which anticipated Dr. Mackett's presentations.

The Declaration by Dr. Buller (D16), who also attended the CSH meeting, merely states that his understanding was and is that the data presented at the meeting were confidential. His second statement of relevance, that he does not know any individual who did not accord confidentiality to the presentations and abstracts from the meetings is again a very personal and very limited view of what actually happened after the meeting, as is demonstrated by the enclosed Declaration by Dr. Aubertin (D32).

2.1.1.4 In conclusion, the above data and arguments leave, according to our view, not a shade of doubt that claim 1 is not patentable for lack of novelty.

2.1.2 Inventive step of claim 1

Even if the Opposition Division comes, contrary to our firm belief, to the conclusion that the contested patent is novel vis-á-vis the prior art, we nevertheless believe that none of the claims is patentable for lack of inventive step.

2.1.2.1 According to the Patentee, the technical problem as reflected by the features of claim 1 was "to deliberately employ pox virus transcriptional regulatory sequences to control the expression of a foreign gene in the recombinant pox virus. To ensure that the pox virus transcriptional regulatory sequence was free to control expression no non-pox virus transcriptional regulatory sequences were placed between the foreign gene and the pox virus transcriptional regulatory sequence"; see petition of Patentee, page 3, third paragraph.

If we assume, for the sake of argument, that the Opposition Division follows the Patentee's arguments and definition of the technical problem, and regards feature (c) of claim 1 not disclosed by any of the prior art discussed in section 2.1.1, supra, then claim 1 is nevertheless unpatentable for lack of inventive step.

2.1.2.2. We certainly hold the view that all the other features of claim 1 are directly disclosed in Panicali (D3) which we regard as the closest prior art document[5]. This is also true for the feature that the coding region of the foreign gene is under the control of a vaccinia TRS; we refer the Opposition Division to Table II, supra and the clear cut analysis of Dr. Hruby on this item; see enclosed declaration at section 16. The technical problem arising from Panicali (D3) was therefore to remove any DNA sequence that would operate in another organism/virus than vaccinia virus such as in the HSV system as a promoter from the foreign gene in order to ensure the direct and unambiguous control of the foreign gene by the vaccinia TRS. The solution to said technical problem was obvious to the person skilled in the art, who in the present case is a bench molecular biologist or a team of bench molecular biologists with a strong background in virology at the priority date of the contested patent. As is reflected, for example in the abstract of Weir (D2), various laboratories, for example the one of Dr. Moss were investigating the possibility of using vaccinia virus as a cloning and expression vector. This scientific goal is summarised in the last sentence of the abstract of Weir (D2), on page 1210, which reads:

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5 Panicali (D3) was also regarded the closest prior art document by the Examining Division; see Communication pursuant to Article 96(2) and Rule 51(2) EPC dated August 1, 1989, section 3. Panicali D3 is used herein as the closest prior art document since we presently do not know for certain whether the Opposition Division will accept the presentations by Dr. Mackett at the ASV conference and the CSH conference, respectively, addressed in section 2.1.1.3, supra, indeed as prior art. If this the case (we do not see any convincing reason why the Opposition Division should decide otherwise) then we reserve the right to discuss any of these presentations as the closest prior art.

> "The mapping of the easily selectable vaccinia virus TK gene now opens the way to genetic manipulations that should increase our understanding of vaccinia virus gene expression and facilitate the use of vaccinia virus as an efficient cloning vector for foreign genes."

2.1.2.3 The person skilled in the art, trying in the early 1980's to develop an improved vaccinia expression vector and being confronted with the technical problem posed by Panicali (D3) would naturally turn for a solution of said problem to Weir (D2). This is because Weir (D2) is published in exactly the same technical field, i.e. the field of constructing vaccinia expression vectors and providing components therefor.

Weir (D2) specifically provides the solution to the above technical problem that Patentee now asserts forms the basis for patentability of his alleged invention. Namely, in the passage bridging pages 1213 and 1214 Weir D2 proposes:

> "Specifically, vaccinia DNA sequences within a plasmid can be modified by in vitro mutagenesis or by insertion of foreign DNA prior to transfection. If the TK gene is modified so as to inactivate it, then recombinants can be selected on the basis of BrdUrd resistance in TK cells. Moreover, by attaching the body of a foreign gene to the vaccinia TK promoter, **efficient expression would be expected**. Ultimately, vaccinia recombinants expressing antigens of other viruses might be used as live vaccines."
>
> (Emphasis added)

The person skilled in the art would therefore, by applying this solution proposed by Weir (D2) to the technical problem posed by Panicali (D3) directly and unambiguously arrive at the subject matter of claim 1. Moreover, as is reflected by the highlighted passage "efficient expression would be expected" and the person skilled in the art also had a reasonable, not to say a high expectation that such a construct would indeed lead to the desired result.[6]

Alternatively, the person skilled in the art would have turned for a solution of the technical problem arising from Panicali D3 to Venkatesan D1. This is because Venkatesan D1 clearly discloses the 7.5 kD vaccinia virus promoter "adjacent to" (see title of D1) the coding sequence. Accordingly, the person skilled in the art had a promoter sequence at hand known to drive expression in the vaccinia virus system. Having the statement from Panicali D3 in mind, namely that "vaccinia signals may be opertive for HSV TK expression" (p. 4931, left column, line 4) the person skilled in the art had every reasonable expectation from the combined study of these two prior art documents that the alleged invention as represented by claim 1 would indeed work. Consequently, claim 1 is obvious in the light of Panicali D3 in combination with Venkatesan D1.

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6 We note with surprise that Patentee emphasises that the data represented in, for example, Weir (D2) were obtained in the inventor's laboratory. It appears that Patentee expects a bonus with regard to patentability of his alleged invention since the opponent cites prior art against him which comes from Patentee's own laboratory. Under EPC regulation it is, however, totally irrelevant where prior art data arises from as long as they are fully citable as prior art. This is certainly the case with, for example, documents Venkatesan (D1) and Weir (D2).

2.1.2.4 Nothing more is required under EPC regulations to demonstrate lack of inventive step. Our view is based on the decision T249/88 "Milk Production/MONSANTO", not published in the OJ EPO, but nevertheless a landmark decision for the assessment of inventive step of biotechnology inventions. This decision has repeatedly been confirmed by the Technical Board of Appeal in the meantime.

In section 8 of the reasons for said decisions, the Board correlated the assessment of inventive step with the expectation of success of an experiment that the person skilled in the art had in view of the teachings of the prior art. In particular, the Board held:

> "In the present situation, this imaginary skilled person was provided with a clear hint from the prior art pointing him in the direction of the claimed method, and it was only necessary to confirm experimentally that the highly probable result was in fact obtained. The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious. Absolute predictability, especially in the field of biologically active chemical compounds, is rather exceptional, but inventions relating to such compounds and their administration to living organisms may nevertheless be obvious. However, if such administration were to lead to unexpected results, which is not the case here, this may provide a basis for demonstrating unobviousness."
>
> (Emphasis added)

We submit that this is the situation to be dealt with in the present case. By combining the teachings of Panicali (D3) and Weir (D2), the

person skilled in the art merely confirmed what was reasonably, or, to be more specific, highly to be expected. Insofar, Patentee's statement on page 12, last paragraph that "the person of skill in the art would be directly discouraged from employing pox virus transcriptional regulatory sequences because HSV TK promoters were represented as being functional and were already characterised" is in stark contrast to what the prior art actually teaches.

In this regard, we would also like to mention that Patentee's citation of other documents which were published prior to the priority date of the contested patent and which are interpreted to discourage the person skilled in the art from trying the approach that led to the alleged invention is totally beside the point. This is because the problem-solution approach as practiced by the EPO starts from the closest prior art document which poses the technical problem and then asks whether the solution of said problem was obvious to the person skilled in the art in the light of the teachings from another prior art document. Documents such as Sam (D11) that are not to be regarded as closest prior art and do not contribute to the solution of said problems are therefore irrelevant for the analysis of inventive step.

2.1.2.5 Our firm belief that claim 1 lacks inventive step is also corroborated by the decision T455/91 "Expression of polypeptides in yeast/GENENTECH", not yet published in the OJ EPO, copy enclosed. This decision confirmed the revocation of a patent for lack of inventive step. The main claim of said patent related to

a DNA vector suitable for use in expressing exogenous genes in yeast. In view of the prior art, the Board defined the technical problem underlying the contested patent in the construction of alternative yeast expression vectors suitable for expressing in yeast any exogenous gene of choice; see T455/91, section 5.1.1. The solution to this technical problem - alternative ways of modifications in the region 5' of the coding region of the expressed protein - was regarded as obvious by the Board; see section 5.1.3.8 of the decision.

We hold the view that the reasoning underlying this decision also applies to the present case. Patentee has provided an alternative vaccinia virus-based vector as compared to the prior art vectors. This vector comprises modifications in the region 5' of the coding region of the expressed protein. It was, as has been detailed in T455/91, for an even earlier priority date known at the priority date of the contested patent that with modifications in the upstream sequences - for example, the TRS - modifications in the expression of the gene of interest could be obtained. This is, in the present case, particularly true in view of the teaching of Weir (D2); see our citation from this document in section 2.1.2.3, supra.

2.1.2.6 Accordingly, and in summary, claim 1 is not patentable for lack of inventive step.

2.1.3 Sufficiency of disclosure of claim 1

Patentee has finally tried to refute our arguments set forth in our opposition brief with

regard to insufficiency of disclosure. We again emphasise that the claims in their current breadth are not supported by the description.

2.1.3.1 Patentee's arguments presented under his title "Claim Scope"

2.1.3.1.1 Patentee has used our statement that vaccinia virus is a prototypic virus for the pox virus family to construct an argument that all scientific results obtained with vaccinia virus are readily transferable to all other members of the pox virus family. It is certainly true that vaccinia virus has in the past been used as a model system for pox viruses. It is equally true that many data obtained with the vaccinia virus model system are readily transferable to other pox viruses. However, there may be situations with the use of a model system, that are not superimposable without further ado on other related systems. Exactly this is the case with the teachings reflected by the very general claim language of the present set of claims.

2.1.3.1.2 Patentee has cited post-published scientific literature to show that the teachings of the present set of claims would also function, for example, in a fowl pox virus. In order to substantiate his argumentation, Patentee has directed the Opposition Division's attention to page 126 of Binns (D22).

A closer review of said page, however, merely yields the following statement which could support Patentee's assertions:

"Also, the insertion of foreign genes into fowl pox should be possible using

> the system of homologous recombination which has been developed for vaccinia." (Emphasis added, see Binns (D22), page 126, right column, centre of the last paragraph).

According to our understanding, this statement reflects merely wishful thinking by the authors, but is certainly no indication of any real data obtained at the publication date of Binns (D22), i.e. in 1986, which is four years after the priority date of the contested patent.

Our view is corroborated by the first sentence on page 127 which reads:

> "We are currently in the early stages of vector development which involves the characterisation of fowl pox sequences which control gene expression."

2.1.3.1.3 In conclusion, we are unable to perceive how Binns (D22) can possibly support Patentee's position. We rather hold the view that the person skilled in the art had nothing in his hands at the priority date of the contested patent to actually transfer the data obtained with vaccinia virus to other pox viruses such as fowl pox virus.

2.1.3.1.4 Perhaps even more interesting for the present purposes than Binns (D22) is to review what has actually become of the wishes and scientific goals to be achieved in the future and expressed therein. Although a patent should be workable over the entire claim scope at the filing or priority date thereof, room must nevertheless be given for future developments that rely on the

teachings of said patent. This line of thought has always been supported by the EPO hitherto.

However, if a future development evolves, in contrast to Patentee's expectations, into a different direction, then it may well be that it cannot be subsumed under the claim language any longer. The logical consequence from such a situation is that the scope of such claims is too broad and should appropriately be reduced.

2.1.3.1.5 We submit herewith the document WO89/12684 Binns (D36). Binns (D36) claims an earliest priority of June 24, 1988, which is five and a half years after the priority date of the contested patent. From Binns (D36) the interested reader can directly take the state of the developments that were envisaged by the same research group about two years earlier in Binns (D22). This outcome may be simply summarised in that the data obtained in vaccinia virus were not transferable to fowl pox virus. Instead, Binns et al. filed an own patent application relating to a fowl pox virus-based expression system wherein into non-essential regions foreign genes may be inserted.

Binns (D36) first stated that fowl pox virus belongs to an entirely different genus than vaccinia virus, namely to the avipox viruses; see page 1, lines 25 to 29. This difference in taxonomic classification is reflected by gross dissimilarities in the overall structure of the genome.

For example, when discussing the state of the art, Binns (D36) referred to data obtained by other laboratories as follows:

> "On the other hand, F.M. Tomley, in a talk at the 6th workshop on Pox virus/Iridovirus, Cold Spring Harbour, New York, 24-28 September 1986, described an attempted correlation of an 11.2 kb fragment of FPV DNA, located near one end of the genome, with VV DNA. While she reported 25% amino acid homology between a gene predicting a 48 kd polypeptide, no other match of any significance was found."
>
> (Emphasis added, see Binns D36, page 3, lines 14 to 21)

Additionally, the authors note at page 4, lines 24 to 32:

> "Large differences between the DNA sequence of VV and FPV are to be expected, since the FPV genome is estimated to be at least one third longer than that of VV. It seems likely, from the present knowledge as cited above, that many of the differences between genomes of FPV and VV will be nearer to the terminal than to the centre of the genome. Thus, information about the terminal region of VV is of limited interest in relation to FPV. It has been a problem to locate a well-defined non-essential region other than the TK gene, in fowlpox virus".
>
> (Emphasis added)

We hold the view that this statement by Binns (D36) directly refutes Patentee's argumentation with regard to the transferability of results obtained with vaccinia virus to other pox viruses.

Even the best characterised regions of the genome of vaccinia virus (Binns (D36), page 5, lines 5 to 6) did not allow the allocation of non-essential regions in fowl pox virus on the

basis of a correlation analysis, as is demonstrated by Binns (D36) on page 5, lines 24 to 30:

> "It was not predictable, however, whether the D8 gene would occur in fowlpox virus and if so whether it would be non-essential. Moreover, there was the problem of how to locate the D8 gene in the FPV genome which is relatively unmapped and is much larger than that of VV. Consequently, examination of the vaccinia virus HindIII-D fragment did not indicate how to find further non-essential regions with FPV."
>
> (Emphasis added)

2.1.3.1.6 In summary, post-published data have conclusively shown that the claims were not workable over the whole range claimed at the priority date of the alleged invention. Further inventions, for example, in the case of fowl pox virus had to be made in order to extend the system developed by Moss et al. for vaccinia to other pox viruses.

2.1.3.2 Patentee's arguments presented under his title "Meaning of 'at least'"

2.1.3.2.1 We thank Patentee for the interpretation of the implications provided by the teachings of example 6; see page 11, last paragraph of his petition. Although we do not concur with his interpretation, we find it interesting to read them on the allegations Patentee makes in the above recited chapter.

On page 11, last paragraph, Patentee explains:

> "In order for either of these HBsAg regions to separate the exemplified HBsAg from the pox virus transcriptional regulatory sequence, the regions would have to be located upstream of the coding sequence of the foreign gene, not within the coding region itself."
>
> (Second emphasis added)

Then, on page 16, penultimate paragraph, he goes on to say:

> "For the purposes of further explanation, the clear import of these phrases is that the claimed vector can have one, two or more protein coding sequences of foreign genes, each associated with pox virus transcriptional regulatory sequences, wherein each coding sequence is not separated from its associated pox virus transcriptional regulatory sequence by another transcriptional regulatory sequence [...]."

First, we note that the above statement is merely a selection of possibilities that the reading of claim 1 offers. This is because claim 1 requires "at least one uninterrupted protein coding sequence from a foreign gene" "under the transcriptional control of the regulatory sequence". Thus, the claim clearly envisages that more than one coding sequence is under the control of one and the same pox virus TRS. If we now assume that one of said coding sequences encodes HBsAg, then we have the case that the "DNA binding site" (we believe it is unnecessary to explain that a "DNA binding site" was indeed regarded a TRS by the person skilled in the art at the priority date of the contested

patent) separates a coding sequence located 3' from the HBsAg coding sequence from the pox virus TRS. Thus, if the Opposition Division concurs with Patentee's view that the HBsAg DNA binding site is indeed a TRS in a vaccinia virus environment, then the above recited construct does clearly not fall under the scope of the present set of claims.

2.1.3.2.2 In addition, we still hold the view that the possibilities proffered in our opposition brief and which are discussed in the above recited section by Patentee, all read on the present set of broad claims and are not merely a hypothetical scenario.

2.1.3.2.2 In summary, the contested patent comprises a number of embodiments which are clearly incompatible with the broad language of the present set of claims. This is in particular true, if the Opposition Division shares Patentee's view that DNA sequences functioning as TRS only outside a vaccinia environment are indeed to be regarded as TRS in said vaccinia environment in the context of the contested patent. In this case we believe that the claim language must be adapted accordingly.

2.1.3.3 Patentees assertions presented under his title "Intervening Nucleotides"

As has been detailed in section 2.1.1 supra, the constructs described in Panicali (D3) and Paoletti (D7) do not comprise a TRS between the vaccinia TRS and the HSV TK coding region. They merely constitute a number of intervening

nucleotides and insofar there exists no difference between the prior art vectors and the claimed vectors. Nothing more needs to be added about this issue.

2.2 **CLAIMS 2 TO 16**

The patentability of claims 2 to 16 depends on the patentability of the main claim. Since claim 1 is not patentable, the remaining claims must share its fate. For a detailed discussion of the subject matter of said claims and their lack of patentability, we refer the Opposition Division to sections 5.2 to 5.14 of our opposition brief.

3. **CONCLUSION**

Patentee's argumentation for defending patentability of the claims as ~~granted~~ must fail in view of the above.

For the same reason as detailed in section 7 of our opposition brief, the contested patent should be revoked in full.

Renate Barth

Dr. Renate Barth
European Patent Attorney

Encl.: as stated above